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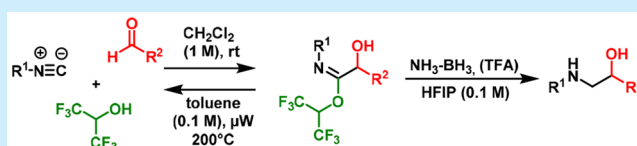
Hexafluoroisopropanol as the Acid Component in the Passerini Reaction: One-Pot Access to β -Amino Alcohols

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S Supporting Information

ABSTRACT: A new Passerini-type reaction in which hexafluoroisopropanol functions as the acid component is reported. The reaction tolerates a broad range of isocyanides and aldehydes, and the formed imidates can be reduced toward β -amino alcohols under mild and metal-free conditions. In addition, the imide products were shown to undergo an unprecedented retro-Passerini-type reaction under microwave conditions, providing valuable mechanistic information about the Passerini reaction and its variations.

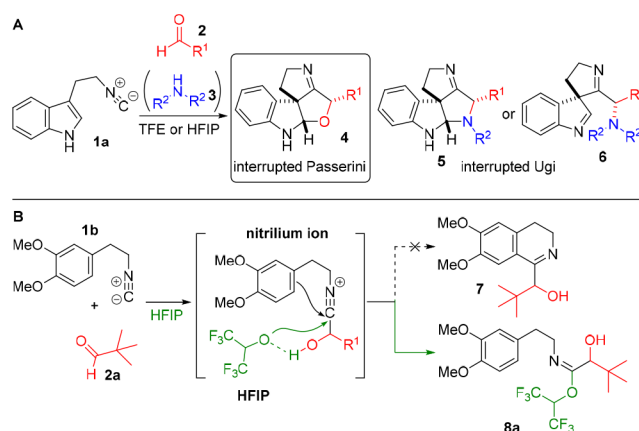


Multicomponent reactions (MCRs) are widely recognized as important tools to create high molecular diversity and complexity in an efficient manner.¹ MCRs combine three or more reactants in a single operation to afford products that contain essentially all of the atoms of the starting materials. Within this field, isocyanide-based multicomponent reactions (IMCRs) have claimed a dominant position as a result of the ambiphilic character of the isocyanide functionality.² In 1921, Passerini discovered the first IMCR, i.e., the reaction between isocyanides, aldehydes, and carboxylic acids to give α -acyloxy carboxamides.³ Forty years later, Ugi cleverly expanded this methodology by simply including an amine, thereby creating a four-component reaction affording peptoid scaffolds.⁴

Even though the discovery of both the Passerini and Ugi reaction dates back more than half a century, current research continues to provide new applications and new variations of these flexible reactions.⁵ Next to postcondensation modifications of traditional Passerini and Ugi products, strategies for the development of MCR variations can be based on single reactant replacement (SRR) or diverting or interrupting the usual reaction pathway.⁶ For IMCRs, the latter mainly involves the reactivity of the nitrilium ion intermediate.

We recently showed that in the interrupted Ugi (or Passerini) reaction of tryptamine-derived isocyanides, the nitrilium ion could be intercepted by the nucleophilic C3 position of the indole moiety, generating highly congested, sp³-rich polycyclic indolines 4–6 (Scheme 1A).⁷ An important feature of this method was the use of the fluorinated protic solvents 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP). The strong hydrogen bond-donating properties and low nucleophilicity of these solvents proved ideal for activation of the imine and stabilization of the nitrilium ion.⁸ In continuation of our work in this area, we aimed to expand this concept to other electron-rich arenes in Passerini- and Ugi-type reactions. When the reaction of 3,4-

Scheme 1. Novel Passerini-Type Reactions



dimethoxyphenethyl isocyanide (1b) and pivalaldehyde (2a) was performed in HFIP as the solvent, intermolecular HFIP addition (to give 8a) surprisingly outcompeted the Bischler–Napieralski cyclization (leading to 7) despite the nucleophilic character of the 3,4-dimethoxyphenyl moiety (Scheme 1B).^{9,10} This serendipitous result prompted us to further investigate this Passerini-type reaction.

Replacing the carboxylic acid in the Passerini reaction by other acid components has been previously demonstrated by several groups.¹¹ However, these reactions typically involve an irreversible Mumm- or Smiles-type rearrangement after the imide formation, generating a thermodynamically favored amide product. Alternative acid components include electron-deficient (hetero)aromatic alcohols.^{5b} Given its comparable pK_a (9.3 vs ~7–9 for phenol derivatives), HFIP plausibly

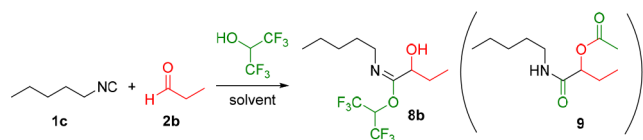
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undergoes a similar addition to the nitrilium ion, which produces a stable imidate **8** that cannot undergo a Mumm-type rearrangement.¹² As these imidates could be considered chemical equivalents of the nitrilium ion synthon, we decided to further investigate this reaction.

We began our optimization with *n*-pentyl isocyanide (**1c**) and propionaldehyde (**2b**) as the benchmark substrates (Table 1). To our surprise, no product formation could be observed

Table 1. Optimization of Passerini-Type Reaction^a



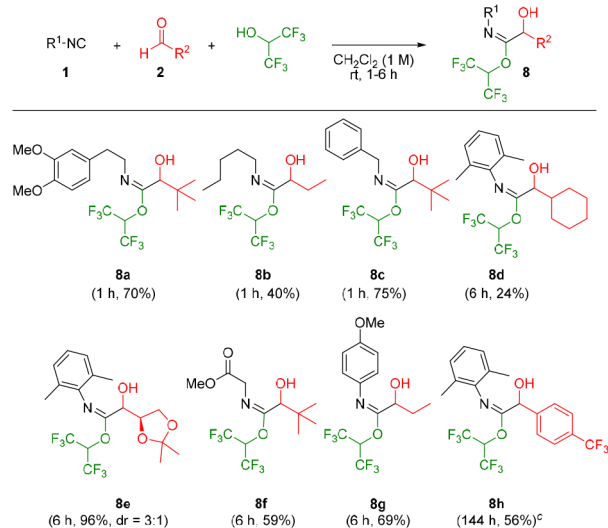
entry	temp (°C)	[1c] (M)	solvent	time (h)	HFIP (equiv)	yield ^b (%)	8b / 9
1	rt	0.1	HFIP	20		0	
2	rt	1	HFIP	20		0	
3	rt	1	CHCl ₃	20	3	0	
4	rt	1	CH ₂ Cl ₂	20	3	58	100:0
5	rt	1	CH ₂ Cl ₂	1	3	82	100:0
6	rt	1	CH ₂ Cl ₂	1	10	82	100:0
7	40	1	CH ₂ Cl ₂	1	3	62	100:0
8 ^c	rt	1	CH ₂ Cl ₂	1	3	>99	0:100

^aStandard conditions: propionaldehyde (0.65 mmol), *n*-pentyl isocyanide (0.5 mmol), and HFIP in solvent, stirred at the indicated temperature and time. ^bBased on NMR analysis with 2,5-dimethylfuran as internal standard. ^cWith 1.2 equiv of AcOH.

by ¹H NMR after subjecting the reactants to the initial conditions (entries 1 and 2). We reasoned that HFIP might be too acidic as a solvent, leading to decomposition of the isocyanide and/or the imidate product rather than activation of the aldehyde. When we switched to CH₂Cl₂ as the solvent with a moderate excess of HFIP (3 equiv), the desired product **8b** was obtained in 58% yield after 20 h and only 37% after 66 h (entry 4), supporting our hypothesis. We then started monitoring conversion over time by ¹H NMR analysis. This experiment revealed that our reaction reached its optimal yield after only 1 h. Although the isocyanide was not completely consumed after 1 h (entry 5), longer reaction times led to lower yields (based on internal standard), most likely as a result of product decomposition. Increasing the stoichiometry of HFIP (entry 6) or the temperature (entry 7) did not lead to improved yields. To evaluate the chemoselectivity of the reaction, we conducted a competition experiment between HFIP and acetic acid, which led to quantitative conversion to the classical Passerini product **9** within 1 h (entry 8).

Having optimized the conditions, we moved our focus toward the scope of this reaction. We were pleased to see that all isocyanides were efficiently converted to the Passerini-type product (Scheme 2), with the exception of *tert*-butyl isocyanide. When the reaction was performed in CD₂Cl₂ and monitored by ¹H NMR analysis, competition between product formation and decomposition was observed. Imidates derived from *t*BuNC are relatively basic, leading to increased decomposition via the protonated imidate.¹³ Another interesting observation is the relation between isocyanide nucleophilicity and product stability. Less nucleophilic isocyanides needed 6 h to reach maximal yields; however, these products showed less decomposition over time. This can be explained

Scheme 2. Scope of the Passerini-Type Reaction^{a,b}



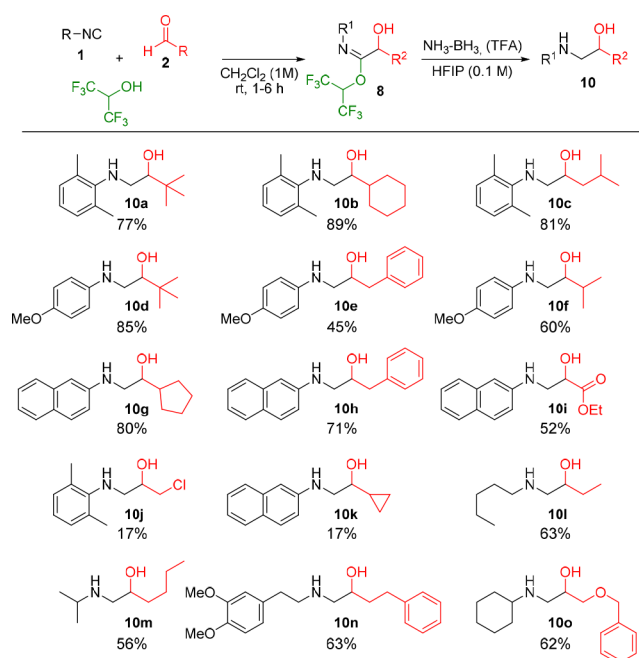
^aStandard conditions: isocyanide (1 mmol), aldehyde (1.3 mmol), HFIP (3 mmol) in CH₂Cl₂ (1 M), rt. ^bIsolated yields. ^cHFIP (0.1 M) was used as the solvent.

by their lower basicity, making degradation pathways less favorable. As for the aldehyde scope, aliphatic aldehydes underwent isocyanide addition effectively, though less reactive aromatic aldehydes and ketones proved to be beyond the scope of this method. Only the relatively reactive *p*-(trifluoromethyl)benzaldehyde reacted to give the product (**8h**), albeit in HFIP as the solvent with 144 h of reaction time.

Having established the limitations of this novel Passerini-type reaction, we investigated the possibility to further diversify these products. Given our earlier experience in Passerini/reduction sequences to valuable β -amino alcohols, we aimed to achieve a similar procedure.¹⁴ We started this endeavor with aromatic imidate **8i**, given its comparably low electrophilicity. After some optimization of the reaction conditions, we found that treatment with BH₃·NH₃ (3 equiv) and TFA (5 equiv) in HFIP gave the highest yield (for details, see the Supporting Information). Due to the higher basicity of imidates derived from aliphatic isocyanides, addition of TFA was not necessary to activate the imidate in these cases.¹⁵ Pleasingly, the two steps could be combined in a one-pot sequence given the compatible conditions.

A broad range of isocyanides and aliphatic aldehydes were screened in this Passerini/reduction method (Scheme 3). Moderate to excellent yields of amino alcohols **10a–k** could be obtained using aromatic isocyanides. Even α -heterosubstituted and highly electrophilic aldehydes smoothly reacted to give the desired product. Surprisingly, even chloroacetaldehyde, a usually problematic reactant in Passerini-type reactions, was converted to the corresponding amino alcohol **10j**, albeit in only 17% yield. Aliphatic isocyanides also exhibited clean conversion, however, the resulting products **10l–o** were generally obtained in slightly lower yields. This can be attributed to the lower stability of these imidates in HFIP, leading to competition between β -amino alcohol formation and imidate decomposition. Nevertheless, it is noteworthy that these reactions generally gave higher isolated yields in this one-pot, two-stage sequence compared to the corresponding imidate synthesis alone (cf. imidate **8b** and β -amino alcohol

Scheme 3. Scope of the One-Pot β -Amino Alcohol Synthesis^{a,b}

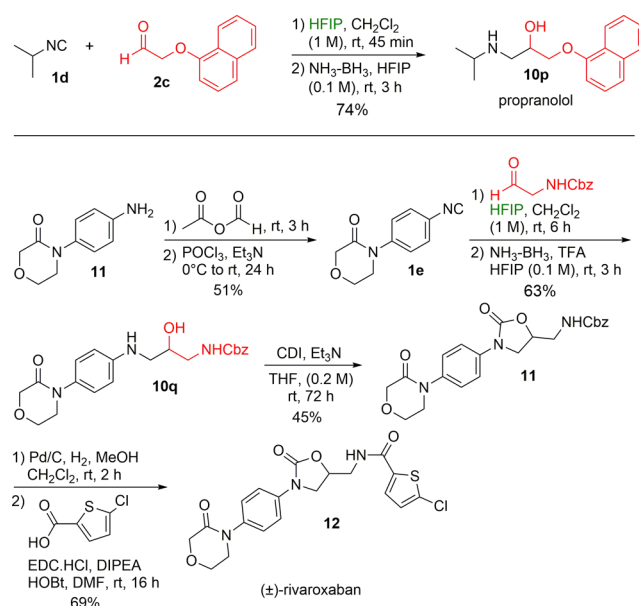


^aStandard conditions: isocyanide (1 mmol), aldehyde (1.3 mmol), HFIP (3 mmol) in CH_2Cl_2 (1 M), rt, next diluted with HFIP (0.1 M), then $\text{BH}_3\cdot\text{NH}_3$ (3 mmol) and TFA (5 mmol). ^bIsolated yields. ^cNo TFA.

10l). This can again be rationalized by the stability issues of these imidates.

As the β -amino alcohol moiety is a structural motif frequently appearing in APIs, we sought to apply the developed methodology in the synthesis of representative pharmaceuticals. This was successfully achieved with the synthesis of propranolol (10p) and (\pm)-rivaroxaban (12, Scheme 4). Propranolol, a β blocker used in the treatment of heart disease,¹⁶ was readily accessible by reaction of (1-

Scheme 4. Synthesis of Propranolol and (\pm)-Rivaroxaban



naphthyloxy)acetaldehyde (2c) and isopropyl isocyanide (74% yield). The reductive Passerini-type reaction of 1e (readily accessible from commercial 11) and (Cbz-amino)-acetaldehyde smoothly afforded 10q, which was further converted to (\pm)-rivaroxaban (12) in three straightforward steps. These applications highlight the robustness of this Passerini/reduction method, which is a mild extension of our earlier work.¹⁴

We then shifted our attention back to our initial attempt to synthesize 3,4-dihydroisoquinoline 7. Given the potential electrophilicity of imidates, and with the Bischler–Napieralski reaction in mind, we considered the possibility of converting imidate 8a to dihydroisoquinoline 7. Unfortunately, treatment with Brønsted or Lewis acids only led to decomposition or imidate hydrolysis. However, when we subjected 8a to microwave irradiation (200 °C, 10 min) under neutral conditions, we surprisingly observed full conversion back to isocyanide 1b. In toluene- d_8 under the same conditions, using 2,6-dimethylfuran as an internal standard, we could clearly observe reformation of all the reactants of the initial Passerini-type reaction (1b, 2a, and HFIP) by ^1H NMR analysis. We were intrigued by the unprecedented reversibility of this Passerini-type reaction, not in the least because computational studies have shown that imidate formation is highly exothermic in both Passerini and Ugi reactions.¹⁷ To evaluate the generality of this retro-Passerini reaction, we selected a small set of imidates (8c,d,f–h) and subjected them to microwave irradiation (200 °C) in 10 min cycles to determine the conversion over time (Table 2).¹⁸ As anticipated, imidate 8c

Table 2. Reversible Passerini-Type Reaction^a

compd	time (min)	conv ^b (%)	compd	time (min)	conv ^b (%)
8c	10	83	8g	240	84
8d	90	67	8h	270	77
8f	60	65			

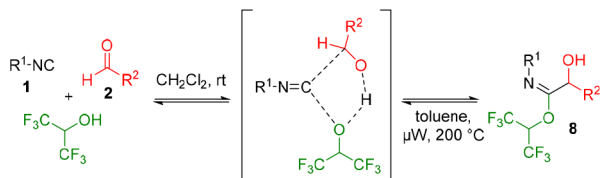
^aStandard conditions: 8 (0.1 mmol) in toluene- d_8 (0.1 M) under microwave irradiation in 10 min cycles at 200 °C. ^bMonitored by ^1H NMR analysis with 2,5-dimethylfuran as internal standard.

also showed near complete conversion (83%). Interestingly, aromatic R^1 as well as R^2 substituents led to considerably slower retro-Passerini reaction. Although full conversion was not reached, a clear trend in reaction rate could be observed between these imidates. Retro-Passerini reaction of imidates 8g and 8h showed clear first order kinetics, as expected for a unimolecular process. The retro-reaction of imidate 8d reached a steady state after 40 min, possibly reflecting a thermodynamic equilibrium under these conditions. After the samples were allowed to sit for 2 weeks at room temperature, all of the crude mixtures were reconverted to the corresponding imidates 8, with the exception of 8d and 8h.

Theoretical studies have already provided some insight in the conventional Passerini reaction, mainly focusing on the involvement of a nitrilium ion intermediate. Morokuma et al. proposed a mechanism including this nitrilium intermediate.^{17c} Our results on this retro-Passerini-type reaction, however, rather suggest a more concerted mechanism, considering the electrophilicity of the nitrilium ion and its resulting propensity

to undergo Bischler–Napieralski-type cyclizations.^{9,19} The formation of a nitrilium ion suggests that fragmentation of the C–CN⁺R bond would outcompete nucleophilic addition of electron-rich arenes (as in imidates **8f** and **8a**). Since the resulting Bischler–Napieralski product is not detected (not even in trace amounts) we believe that a concerted mechanism is more likely in both the forward Passerini-type reaction and the reverse reaction (Scheme 5). The effect of the conditions

Scheme 5. Concerted Mechanism of the Passerini Reaction



on the directionality of the reaction can be rationalized by thermodynamic considerations. As $\Delta G = \Delta H - T\Delta S$, the enthalpic factor dominates the outcome of the reaction at room temperature, while at 200 °C the entropic factor becomes more important, favoring the reverse reaction.

In conclusion, we report a Passerini-type reaction toward α -hydroxy imidates with HFIP as a novel acid component. By combining this procedure in one pot with a subsequent reduction step, we efficiently synthesized a series of β -amino alcohols. The scope of this procedure proved to be complementary to our previous Passerini/reduction strategy.¹⁴ In addition, the utility of this mild transformation was demonstrated by the synthesis of the two APIs, propranolol and (\pm)-rivaroxaban. Finally, we showed these α -hydroxy imidates undergo an unprecedented retro-Passerini-type reaction under microwave irradiation. This observation provides new insight into the Passerini reaction and contributes to a better mechanistic understanding of isocyanide chemistry in general.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01561.

Experimental details, characterization data, and copies of ¹H and ¹³C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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